Genetic differences may help explain inconsistent effectiveness of anti-HIV drug

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Research with human tissue and cells suggests that genetic variations, in addition to failure to comply with treatment regimens, may account for some failures of an anti-HIV drug to treat and prevent HIV infection.

In a report described online today in the journal *EBioMedicine*, investigators at Johns Hopkins found that tenofovir, marketed as Viread, is processed differently according to cell location, so that if the drug is eventually marketed as a topical gel, it could work differently depending on whether it is applied to the vagina or the rectum.

Tenofovir has been approved since 2001 by the U.S. Food and Drug Administration to treat HIV. It is also a component of Truvada, a drug that was approved in 2012 as an oral prophylactic for use in preventing HIV infection.

"If confirmed by further studies, our results suggest that in the future, before prescribing tenofovir to a patient, a doctor could order genetic testing and know in advance if it works, and prescribe a different drug if it won't," says Namandje Bumpus, Ph.D. , associate professor of medicine at the Johns Hopkins University School of Medicine.

Bumpus and her colleagues focused their research on a search for the human enzymes that convert tenofovir from its original form to an activated one that combats HIV. Previous studies had revealed that the key to such activation is the addition of two molecules known as phosphate groups, she says.

Working with blood and tissue from healthy research subjects, her team "knocked out" genes for phosphate-adding enzymes one by one, then exposed the tissues' cells to tenofovir to test whether they were able to activate the drug.

To their surprise, says Bumpus, they learned that the enzyme that added the second phosphate to activate the drug in the blood and vaginal tissues, pyruvate kinase, was different from that which performed the second activation step in the colorectal tissues, known as creatine kinase.

In further experiments, the research team sequenced the genes of 142 women who had participated in a clinical trial of tenofovir to look for genetic variations that might have affected the function of pyruvate kinase, creatine kinase or the enzyme that performed the first activation step in all of the cells, adenylate kinase 2. They found 71 such variants, several of which a computer model predicted would make the enzyme ineffective. In all, 8 percent of the women had genetic variants that were likely to make them unable to convert tenofovir to its activated form.

"Tenofovir has been shown in trials to be very effective, so when it doesn't work, researchers and clinicians tend to assume the individual just wasn't taking the drug as directed," Bumpus says. "That is probably true in most cases, but in others, it's possible that genetic variation is actually at fault."

The team's next step, Bumpus says, will be to design a clinical trial to confirm the association between specific variants and how well the drug works.

Provided by Johns Hopkins University School of Medicine

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